

Editorial: Expression of HLA antigens in the cornea

The paper by El-Ashar and colleagues this month (p 587) is unlikely to attract more than a passing glance from most clinicians, yet it centres on a subject that already has considerable clinical relevance, and it sets the scene for an examination of recent developments in corneal immunology, particularly transplantation. Its main conclusion is that class II human leucocyte antigens (HLAs) can be expressed on the corneal epithelium and endothelium, and we need to examine why this is important, beginning with a summary of the role of class I and class II antigens.

Class I antigens, encoded by three main regions (HLA A, B, and C), are glycoproteins that are formed on the surface of all nucleated cells. Their natural function is that they are required for the successful interaction of T lymphocytes of the killer subset (CD8+) with self cells which have foreign antigen (particularly viral antigens) on their surface: the CD8+ cells react with self plus antigen ('dual recognition') to produce cell lysis. Foreign (donor) class I antigens in a transplant can be treated in a similar way, specific CD8+ cells seeing them as 'self plus x', with consequent damage to the graft. A good deal of painstaking work has shown that some degree of compatibility between donor and host class I antigens (tissue matching) does, as expected, slightly reduce the incidence of corneal graft rejection in high-risk patients, but there are so many class I antigens that a really good match is highly improbable. Low-risk patients have such a good prognosis that the expensive and time consuming process of matching is not justified for the doubtful benefits.

Class II HLA antigens (encoded by the D region) are also glycoproteins, but they are normally more restricted to cells concerned directly with immune responses, such as B cells and macrophages and the antigen presenting cells in the corneal epithelium (Langerhans cells) and stroma (interstitial dendritic cells). Their natural function, again by 'dual recognition', is to guide helper T (CD4+) cells in their interaction with antigen presenting cells, and with B cells, so that this interaction is normally (and quite appropriately) restricted to them. It would usually be unsatisfactory if other cells triggered these reactions. However, it has been realised recently that this can sometimes occur. Liver cells for example can express class II antigens under the influence of interferon during inflammation, and

we now learn from El-Ashar and colleagues that corneal epithelial and endothelial cells can do just the same. This has a particularly important bearing on transplantation, as well as taking us further towards unravelling the pathogenesis of some types of corneal inflammatory disease.

In the unnatural milieu of transplantation it appears that donor class II antigens, borne on the antigen-presenting cells in the corneal disc, are the main stimulus to the afferent limb of the allograft reaction: they induce CD4+ cells to promote the differentiation of CD8+ cells (via lymphokines such as interleukin 2) which may then destroy the graft. Host antigen presenting cells may be able to initiate the afferent limb by processing donor class I antigens, but this is a much weaker stimulus. It does indeed appear that class II (HLA D) antigen matching reduces the incidence of rejection, and so may attempt at reducing the class II antigenic load in the donor. Various experimental methods, and the procedure of organ culture for donor corneal storage, reduce the Langerhans cell count and probably reduce the incidence of rejection. But, surprisingly, a carefully conducted prospective trial by Stulting and colleagues¹ (published since the paper by El-Ashar and colleagues was submitted) showed that removal of the donor epithelium (and hence the Langerhans cells) did not. Perhaps too many class II bearing cells remain in the stroma.

It is all the more worrying to learn now that class II antigens could be expressed both by the corneal epithelial and endothelial cells in states of inflammation. Either this could lead to rejection *de novo*, if the inflammation was not caused by it in the first place—and this could be one further explanation for the observation that rejection so often seems to follow inflammatory disease such as herpes. Or it could lead to a spiral of worsening rejection if rejection was the original cause of the inflammation.

How fortunate we are in ophthalmology that topical steroids are usually so effective at all stages of the rejection process. But perhaps we should be even readier to use them preventively—particularly before, as well as after, the graft.

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Reference

- 1 Stulting RD, Waring GO, Bridges WZ, Cavanagh HD. Effect of donor epithelium on corneal transplant survival. *Ophthalmology* 1988; 95: 803-12.